Trends and costs of stereotactic body radiation therapy in metastatic non-small cell lung cancer

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Background: The purpose of this study is to describe stereotactic body radiation therapy (SBRT) use, outcomes, hospitalizations and costs compared to patients receiving chemotherapy among patients with metastatic non-small cell lung cancer (NSCLC).

Methods: Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we identified patients aged ≥66 with metastatic NSCLC treated with SBRT as first-line treatment between 2004 and 2014. Multivariable logistic regression identified covariates associated with SBRT. Overall survival (OS) between SBRT and chemotherapy was compared using the Kaplan-Meier estimator and Cox proportional hazards regression. To compare hospitalizations and associated costs, we matched patients treated with SBRT to those with comparable prognostic factors receiving chemotherapy.

Results: We identified 215 patients with metastatic NSCLC who received SBRT and 12,486 patients who received chemotherapy as first-line treatment. SBRT use increased from 0.5% to 3% and was associated with older age, female sex, poor disability status, and lower T- and N-stage. OS increased with SBRT, female sex, higher income and decreased with higher Charlson Comorbidity Score ≥2, poor disability status, higher T-stage and higher N-stage. Among a matched sample, SBRT patients underwent fewer hospitalizations *vs.* chemotherapy patients (73% *vs.* 81%, P=0.02). Among those hospitalized, SBRT patients incurred higher hospitalization costs ($33,063 *vs.* $23,865, P<0.001) but costs per month of survival were similar.

Conclusions: SBRT is increasing among Medicare patients with metastatic NSCLC. Our findings suggest that SBRT may play a role in management of select metastatic NSCLC patients in addition to standard-of-care chemotherapy.

Keywords: Stereotactic body radiation therapy (SBRT); Surveillance, Epidemiology, and End Results-Medicare (SEER-Medicare); costs; hospitalizations; metastatic lung cancer

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Introduction

An estimated 228,820 new cases of lung cancer were expected in the United States in 2020, and lung cancer is the leading cause of cancer deaths (1). Approximately 85% of all cases of lung cancer are non-small cell lung cancer (NSCLC) (2). Oligometastatic disease was first described in 1995 as cancers with a limited number of metastatic deposits (3). Although the precise prevalence of oligometastatic NSCLC is unknown, some series suggest that approximately 50% of NSCLC patients present with disease limited to the primary lung and nodal sites and ≤3 metastases confined to three or fewer organs (4). Up to 40% of patients treated for cure with localized lung cancer will eventually develop metastatic progression (5).

Metastatic NSCLC has traditionally been managed with systemic therapy; however, there is growing evidence that the addition of local therapy to oligometastases improves overall disease control in this population. Multiple retrospective studies have demonstrated longer median overall survival in carefully selected patients who undergo metastasectomy for oligometastatic NSCLC (6-8). Stereotactic body radiation therapy (SBRT) is a form of definitive local therapy that allows for the delivery of anatomically precise, ablative doses of radiation therapy, and is routinely used to treat early stage medically inoperable lung cancer (9). Three randomized phase II studies support the use of SBRT in oligometastatic NSCLC. A randomized phase II by Gomez *et al.* in patients with oligometastatic NSCLC that did not progress after front-line systemic therapy found that SBRT directed at oligometastases prolonged progression-free survival and overall survival (10). Similarly, Iyengar *et al.* showed that the use of consolidative SBRT prior to maintenance chemotherapy nearly tripled progression-free survival in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone (11). Finally, a randomized phase II study by Palma *et al.* found that in patients with controlled primary tumors of various sites, the addition of SBRT improved 5-year overall survival by about 25% (12). These findings need to be validated in phase III trials, which are currently accruing. Outside of clinical trials, which selectively enroll good performance status patients with limited (oligometastatic) disease, the use and outcomes of SBRT among the general metastatic NSCLC population are not known.

While systemic therapy remains the backbone of therapy for metastatic NSCLC, the introduction of new and expensive systemic therapy agents has also raised significant concern regarding their consumption of health care resources (13). Indeed, the overall costs of cancer care in the United States were $183 billion in 2015 and projected to increase 34% to $246 billion by 2030 (14). First-line chemotherapy with paclitaxel, carboplatin and bevacizumab for metastatic NSCLC has been estimated to cost Medicare $90,044 dollars per patient over a 2-year time period (15). Adverse events and hospitalizations are common, as approximately 30% of patients receiving this regimen experience grade 4 toxicity (16). There is growing recognition that hospitalizations represent a substantial proportion of cancer expenditures, primarily related to complications from systemic therapy, such as neutropenia (14). Therefore, characterizing admitting diagnoses and costs from hospitalizations during cancer therapy is warranted.

Currently, the patterns of care utilizing SBRT in elderly metastatic NSCLC patients and the impact on survival are unclear. The impact potential of SBRT use on hospitalizations is also not known, and we hypothesize that improvements in disease control from SBRT may result in more time off chemotherapy, thereby decreasing hospitalizations. The purpose of this project is to describe early SBRT use and its association with survival in patients with metastatic NSCLC, as well as to compare hospitalizations and their costs to a matched subsample of patients receiving chemotherapy using population-based Medicare data in the United States. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1835/rc).

Methods

Data source and identification of cohort

We performed a historical cohort study using the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. The SEER program collects cancer incidence and survival information from population-based cancer registries encompassing 26% of the population of the United States (17). Linked Medicare claims for health care services, and linkage to Medicare claims is available for 93% of the SEER population who are ≥66 years old (18). The study received a "Not Human Subjects" designation from the University of Vermont IRB. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

A total of 116,998 patients ≥66 years diagnosed with stage IV NSCLC diagnosed from January 1, 2004 to December 31, 2013 and enrolled in the Medicare fee-for-service program, linked to claims for treatment and outcomes from January 1, 2003 to December 31, 2014 were identified as potentially eligible for the study. Allowing a full year of Medicare claims prior to cancer diagnosis enables identification of pre-existing co-morbidities and disability scores. Medicare claims codes after diagnosis were used determine initial cancer treatment. Codes for SBRT were introduced in 2004; codes used to identify both SBRT and systemic treatment are in Table S1 (19-21). We excluded patients who were diagnosed with NSCLC on autopsy, had brain metastases, received cancer-directed surgery. We also excluded who died within 30 days of diagnosis and did not receive cancer-directed treatment. Patients were also excluded if they were enrolled in a health maintenance organization (HMO) during the 12 months before and after diagnosis in order to ensure complete Medicare claims record. After all exclusions, there were 12,701 patients eligible for the study: 215 receiving SBRT and 12,486 receiving chemotherapy as initial treatment. Some patients (108 or less than 1% of the overall sample) subsequently received the other treatment and were retained in the study to ensure that the results were representative of treatment provided in real-world clinical settings. These were mostly SBRT patients. Among patients who received SBRT as initial treatment, 24.5% subsequently received chemotherapy. Among patients who received initial chemotherapy, only 0.5% subsequently received SBRT. The follow-up period for survival was from the date of diagnosis of metastatic disease until death, and ranged from 1 to 131 months, with a mean of 17.6 for the SBRT group and 12.7 for the chemotherapy group.

Construction of variables

Data elements in SEER included patient characteristics (age, gender, race, payer, vital status, urban/rural county of residence, zip code) and cancer-related information (stage, grade, histology). Median income was determined by linking the patients' zip codes to their median income in the Zip Code Census File. We obtained hospital characteristics for patients who underwent treatment at a hospital-based outpatient center (profit *vs.* non-profit, whether the center was associated with a teaching hospital, and whether the hospital was an NCI-designated comprehensive cancer center or community cancer center). Specific systemic

therapy regimens and the number of treatment cycles of first- and second-line chemotherapy regimens administered to each patient were determined using algorithms in previous claims-based studies of chemotherapy utilization (22-25).

Comorbidity is an independent prognostic factor in lung cancer and is associated with lower chemotherapy use (26-28). Comorbidity was measured by the use of claims billed between 24 and 3 months before cancer diagnosis. ICD9 codes that appear on inpatient claims or at least two outpatient/physician claims occurring at least 30 days apart were used. Using the comorbid conditions included in the Charlson Index, we computed the NCI Comorbidity Index, which is a cancer-specific version of the Charlson Index (29,30). In addition, disability—a patient characteristic related to comorbidity—has been shown to independently impact healthcare utilization. To control for this potential confounding, we also computed validated claims-based index (the Davidoff index) which is correlated with patient characteristics, including age, and socioeconomic status and is a significant predictor of cancer treatment (31).

Costs

Hospitalization costs for each patient were ascertained from Medicare inpatient claims data. The length of stay, total cost and admission diagnosis were determined for each hospitalization from the date of diagnosis to the date of death, or the end of the follow-up period. For each patient the total number of hospitalizations, total number of days of hospitalization and the total hospital cost were calculated. Adjustment for differences in survival was made by dividing by the number of months of follow-up.

Statistical analyses

Bivariate associations between treatment and the independent variables of interest (time, clinicopathologic characteristics, and comorbidity/age strata), and covariates were assessed using chi squared tests for categorical variables and student's *t*-test for continuous variables. The trend in use of SBRT as first-line treatment over the study period was tested with a Cochran Armitage trend test. Logistic regression was performed to identify variables significantly associated with SBRT use. Overall survival following initial treatment with chemotherapy or SBRT was assessed the Kaplan-Meier estimator. Cox proportional hazards regression was used to compare overall survival
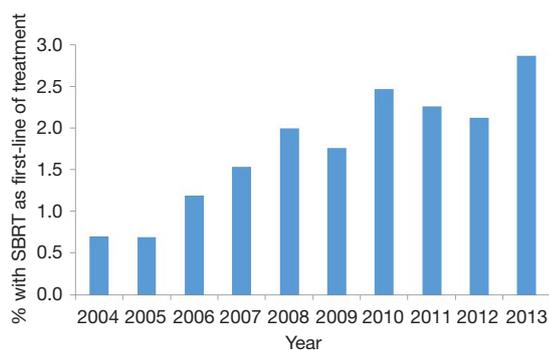
Figure 1 Trends in SBRT use. SBRT, stereotactic body radiation therapy.

in the chemotherapy and SBRT groups after adjustment for demographic and clinicopathologic variables that were significantly associated with survival. Missing data for covariates were included in the regression analysis as separate categories. To compare hospitalizations and their associated costs a subsample of chemotherapy patients who were similar to SBRT patients in terms of age, T, N, disability status and comorbidity status was selected using propensity score matching based on a logistic regression model, with 1:4 nearest neighbor matching without replacement. We then used linear models with matched group as a random effect to compare hospitalizations and their associated costs. Prior to matching, all patients that joined an HMO after diagnosis were excluded. To comply with the SEER-Medicare Data Use Agreement stipulation that cell counts <11 may not be directly reported or be derivable with more precision than "<11", variables presented in a table or figure with a cell count <11 had cell counts for two categories either coarsened or suppressed. Statistical analyses were performed using SAS Version 9.4 statistical software (SAS Institute, Cary, NC, USA). All statistical tests were two-sided with α=0.05.

Results

We observed a significant increase in the use of SBRT as first-line treatment from 0.7% to 3.0% over the study period (*Figure 1*, P<0.001). The median age for the entire sample was 73.0 years (interquartile range, 69–78 years) and comparisons of baseline characteristics in patients receiving SBRT and chemotherapy are shown in *Table 1*. As compared to patients treated with chemotherapy, those who received SBRT as first-line therapy had Charlson Comorbidity

Scores ≥2 (P=0.005), were more likely to be female (P<0.001), had poor disability status (P<0.001), and lower T- and N-Stage (P<0.001). Logistic regression analysis indicated that older age [odds ratio (OR) 1.09 per year, P<0.001], female sex (OR 1.54, P=0.002), poor disability status (OR 2.09, P=0.001), and lower T- and N-stage (P<0.001) were independently associated with SBRT after adjustment for all other covariates (*Table 2*).

The median survival for patients with SBRT as first-line treatment, and chemotherapy alone was 12 and 8 months, respectively (*Figure 2*, log-rank, P<0.001). SBRT was associated with longer overall survival [hazard ratio (HR) 0.72, 95% CI: 0.62–0.83, P<0.001] after adjustment for all covariates significantly associated with overall survival. Covariates independently associated with increased survival included female sex (HR 0.80, P<0.001) and higher income (≥$80,000, HR 0.85, P<0.001), while Charlson Comorbidity Score (≥2, HR 1.09, P<0.001), poor disability status (HR 1.22, P<0.001), higher T-stage (HR 1.31, P<0.001) and higher N-stage (N3, HR 1.21, P<0.001) were associated with decreased survival (*Table 3*). There was a significant interaction (P<0.001) between N-stage and treatment, indicating that the increased survival with SBRT was primarily attributable to patients with N0 disease (HR 0.59, 95% CI: 0.48–0.72).

Among a sample matched on age, sex, Charlson comorbidity Score, disability status, T-stage and N-stage, fewer patients treated with first-line SBRT underwent hospitalization compared to chemotherapy patients (73% *vs.* 81%, P=0.02) (*Table 4*). The mean number of hospitalizations was similar for SBRT and chemotherapy patients, but was significantly lower when normalized by months of survival (0.22 *vs.* 0.28, P=0.009). Although SBRT patients incurred higher total hospitalization costs (mean $24,266 *vs.* $19,213, P=0.008), costs per months of survival were slightly lower and did not differ significantly from chemotherapy patients. Among those who had one or more hospitalizations, the average number of hospitalizations and number of days of hospitalization were significantly higher for SBRT than chemotherapy patients, but not when expressed as per months of survival. Similarly, the total cost of hospitalization was higher for SBRT patients ($33,063 *vs.* $23,865, P<0.001), but the cost per month of survival was nearly the same as for chemotherapy patients ($3,883 *vs.* $3,924, P=0.94). However, the average cost per hospitalization was significantly higher for SBRT patients ($13,647 *vs.* $10,432, P<0.001). Admission diagnoses are listed in Table S2, with the most common diagnoses being

Table 1 Comparison of patients treated initially with SBRT and chemotherapy

Characteristic	SBRT (n=215)		Chemo (n=12,486)		P value
	No.	%	No.	%	
Urban/rural					0.71
Urban	>204	>94.9	12,206	97.8	
Rural	<11	<5.1	280	2.2	
Census tract poverty indicator					0.90
<20% poverty	174	80.9	9,963	79.8	
≥20% poverty	>30	>14.0	2,380	19.1	
Unknown	<11	<5.1	143	1.1	
Charlson Comorbidity Score					0.005
0	68	31.6	4,982	39.9	
1	54	25.1	3,378	27.0	
≥2	93	43.3	4,126	33.0	
Race					0.12
White	192	89.3	10,951	87.7	
Black	>12	>5.6	947	7.6	
Other	<11	<5.1	588	4.7	
Sex					<0.001
Male	95	44.2	7,025	56.3	
Female	120	55.8	5,461	43.7	
Histology					0.94
Squamous	48	22.3	2,816	22.6	
Non-squamous	167	77.7	9,670	77.4	
Disability status					<0.001
Poor	26	12.1	567	4.5	
Good	189	87.9	11,919	95.5	
Derived AJCC 6th ed., T					<0.001
T0/T1	51	23.7	1,199	9.6	
T2	49	22.8	2,879	23.1	
T3	<11	<5.1	740	5.9	
T4	85	39.5	5,850	46.8	
Unknown	>19	>8.8	1,818	14.6	
Derived AJCC 6th ed., N					<0.001
N0	130	60.5	2,608	20.9	
N1	13	6	1,000	8.0	
N2	48	22.3	5,431	43.5	
N3	11	5.1	2,300	18.4	
Unknown	13	6	1,147	9.2	

Table 1 (*continued*)

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Characteristic	SBRT (n=215)		Chemo (n=12,486)		P value
	No.	%	No.	%	
Median Income					0.89
<$40,000	41	19.1	2,505	20.1	
$40,000–59,999	86	40	4,725	37.8	
$60,000–79,999	48	22.3	2,843	22.8	
≥$80,000	>29	>13.5	2,202	17.6	
Unknown	<11	<5.1	211	1.7	
Age at diagnosis, median [IQR]	77 [73–82]		73 [69–78]		<0.001

SBRT, stereotactic body radiation therapy; Chemo, chemotherapy; AJCC, American Joint Committee on Cancer; IQR, interquartile range.

shortness of breath (27%) and pneumonia (20%), with shortness of breath being more common among SBRT patients, and infections being more common among chemotherapy patients (Table S2).

Discussion

To our knowledge, this is the first study to assess the patterns of care of SBRT use in metastatic NSCLC. First-line SBRT use in patients with metastatic NSCLC is increasing and its use was associated with longer overall survival (HR 0.72) compared to patients treated with chemotherapy only. This survival difference persisted despite SBRT patients having a number of poor prognostic characteristics in our sample, including higher Charlson Comorbidity Scores, poor disability status and higher T- and N-stage. It is important to acknowledge that selection bias is likely contributing this observed difference in survival to some extent. This is because detailed information regarding the extent of metastatic disease, or number of metastatic sites, cannot be determined with certainty from the SEER-Medicare data. Therefore, systemic imbalances could exist with regard to metastatic disease burden and its influence treatment patterns. While we minimized selection bias in our comparisons of outcomes, hospitalizations and costs between SBRT and non-SBRT patients by controlling for available confounding variables, additional unmeasured confounders likely exist. An observational study design cannot establish causality, but we have nonetheless observed that early adoption of SBRT was associated with
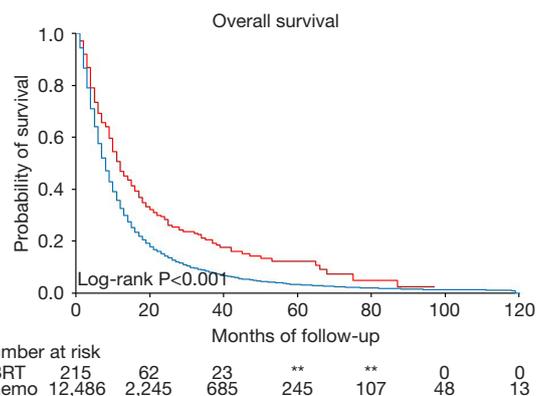
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Table 2 Covariates independently associated with use of stereotactic body radiation therapy

Variables	Adjusted OR	95% CI	P
Age at diagnosis	1.09	1.07–1.12	<0.001
Derived AJCC 6th ed., N			<0.001
N0	Ref.		
N1	0.29	0.16–0.52	
N2	0.21	0.15–0.29	
N3	0.12	0.06–0.22	
NX	0.29	0.16–0.52	
Derived AJCC 6th ed., T			<0.001
T0/T1	Ref.		
T2	0.45	0.30–0.68	
T3	0.33	0.15–0.70	
T4	0.43	0.30–0.62	
TX	0.35	0.21–0.60	
Disability status			0.001
Good	Ref.		
Poor	2.09	1.35–3.25	
Sex			0.002
Male	Ref.	Ref.	
Female	1.54	1.16–2.03	
Charlson Comorbidity Score			0.33
0	Ref.		
1	1.07	0.75–1.54	
≥2	1.27	0.92–1.76	

OR, odds ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer.

Figure 2 Kaplan-Meier curves comparing overall survival by initial SBRT versus chemotherapy treatment regimens. **, suppressed cell count. SBRT, stereotactic body radiation therapy; Chemo, chemotherapy.

improved survival when adjusting for available confounding covariates. Our study thus supports further investigation of SBRT in this population. Indeed, multiple phase III randomized studies assessing the impact of SBRT on survival in metastatic cancer are ongoing (32-34).

Although fewer SBRT patients were hospitalized during follow-up, among those who were hospitalized, the average number of hospitalizations and days of hospitalization were higher in SBRT compared to chemotherapy due to their longer survival. We also observed increased hospitalization costs for those who received SBRT, which is primarily attributable to longer survival. When normalized by months of survival, the number of hospitalizations was lower in the SBRT patients and costs did not differ significantly from the chemotherapy patients. It should be emphasized that this is an observational and not causal relationship, meaning that the observed differences in healthcare utilization may reflect fundamental differences in these population, such as the extent of disease. However, it is notable that the average cost per hospitalization was significantly higher in the SBRT patients. It is not entirely clear why this is the case, but is possible that the observed increased hospitalization costs reflect more complex management of treatment-related complications. As more chemotherapy patients were admitted with intercurrent infections and SBRT patients were admitted with shortness of breath (possibly pneumonitis), it is plausible that SBRT-related complications different from chemotherapy, leading to different care needs for hospitalizations. Supporting this hypothesis, in the SABR-COMET phase II randomized trial, SBRT was associated with a 20% absolute increased risk of grade ≥2 adverse events (12). Despite increased toxicity, multiple cost-effectiveness analyses of available data have thus far shown SBRT to be a cost-effective treatment for metastatic cancer (35-37). This is consistent with our finding of somewhat lower costs per months of survival for SBRT.

Our finding that SBRT use is higher among patients with increased age and poor disability warrants discussion. In the three aforementioned randomized phase II of SBRT in oligometastatic cancer, the median age of SBRT patients was 64–67 years, with Eastern Cooperative Oncology

Table 3 Associations of treatment and covariates with overall survival

Variables	Unadjusted			Adjusted		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
First-line treatment			<0.001			<0.001
Chemo	Ref.			Ref.		
SBRT	0.67	0.57–0.77		0.72	0.62–0.83	
Urban/rural			0.006			–
Rural	Ref.			–	–	
Urban	0.84	0.75–0.95		–	–	
Census tract poverty indicator			0.26			–
≥20% poverty	Ref.			–	–	
<20% poverty	0.96	0.92–1.01		–	–	
Unknown	1.02	0.85–1.20		–	–	
Charlson Comorbidity Score			<0.001			<0.001
0	Ref.			Ref.		
1	1.03	0.99–1.08		1.03	0.99–1.08	
≥2	1.11	1.07–1.16		1.09	1.05–1.14	
Race			<0.001			<0.001
White	Ref.			Ref.		
Black	0.98	0.92–1.05		0.93	0.87–1.00	
Other	0.81	0.75–0.89		0.80	0.73–0.87	
Sex			<0.001			<0.001
Male	Ref.			Ref.		
Female	0.80	0.77–0.83		0.80	0.78–0.83	
Histology			0.003			–
Non-squamous	Ref.			–	–	
Squamous	1.07	1.02–1.11		–	–	
Disability status			<0.001			<0.001
Good	Ref.			Ref.		
Poor	1.16	1.07–1.26		1.22	1.12–1.33	
Age at diagnosis (per 1 year increase)	1.009	1.006–1.013	<0.001	1.012	1.008–1.015	<0.001
Median Income			<0.001			<0.001
<$40,000	Ref.			Ref.		
$40,000–59,999	0.95	0.90–0.99		0.96	0.91–1.01	
$60,000–79,999	0.90	0.85–0.95		0.91	0.86–0.96	
≥$80,000	0.84	0.79–0.89		0.85	0.80–0.90	
Unknown	0.98	0.84–1.12		0.98	0.85–1.13	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Unadjusted			Adjusted		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
AJCC 6th ed., N			<0.001			<0.001
N0	Ref.			Ref.		
N1	1.18	1.10–1.27		1.16	1.07–1.25	
N2	1.26	1.20–1.32		1.24	1.18–1.30	
N3	1.22	1.16–1.30		1.21	1.15–1.29	
NX	1.18	1.10–1.27		1.16	1.08–1.25	
AJCC 6th ed., T			<0.001			<0.001
T0/T1	Ref.			Ref.		
T2	1.21	1.13–1.29		1.17	1.09–1.25	
T3	1.37	1.25–1.50		1.32	1.20–1.45	
T4	1.34	1.26–1.43		1.31	1.23–1.40	
TX	1.27	1.18–1.36		1.25	1.15–1.35	

CI, confidence interval; Chemo, chemotherapy; SBRT, stereotactic body radiation therapy; AJCC, American Joint Committee on Cancer.

Table 4 Hospitalizations and their associated cost for SBRT and chemotherapy patients matched on age at dx, T, N, disability status (poor, good), sex, and Charlson Comorbidity Score (0, 1, ≥2)

Variables	SBRT (N=213)	Chemo (N=631)	P value
Patients with ≥1 hospitalization, n [%]	156 [73]	509 [81]	0.02
All patients in matched sample, mean ± SE			
Number of hospitalizations	2.00±0.14	1.90±0.09	0.52
Hospitalizations per month of survival	0.22±0.02	0.28±0.01	0.009
Total hospitalization cost ($)	24,266±1,697	19,213±1,058	0.008
Cost per month of survival ($)	2,843±360	3,165±209	0.44
Hospitalized patients only, mean ± SE			
Number of hospitalizations	2.73±0.16	2.36±0.09	0.04
Hospitalizations per month of survival	0.29±0.03	0.35±0.01	0.07
Number of days of hospitalization	16.64±1.11	13.38±0.63	0.01
Days of hospitalization per month of survival	1.87±0.24	2.25±0.13	0.16
Total cost of hospitalization ($)	33,063±1,947	23,865±1,128	<0.001
Cost per hospitalization ($)	13,647±735	10,432±407	<0.001
Cost per month of survival ($)	3,883±452	3,924±250	0.94

SBRT, stereotactic body radiation therapy; dx, diagnosis; Chemo, chemotherapy; SE, standard error.

Group performance status of 0–2 (10-12). Our study is limited to Medicare-eligible patients and hence an older population. Older, more frail patients receiving SBRT in our population could suggest that outside of clinical trials, SBRT is being used in patients who cannot tolerate systemic therapy. Regardless, it is plausible that survival advantage SBRT may be underestimated in our study, given the differences in baseline characteristics we observed compared to the phase II studies.

This study has substantial strengths. It used data representing real-world settings and sophisticated quantitative methods to determine the trends, determinants, and outcomes of treatment in metastatic lung cancer patients. Our results provide useful survival information for this population. Estimates of hospitalizations and costs in this manuscript are novel contributions to the literature and may help guide policy and clinical decisions pertaining to the diffusion and use of SBRT in this patient population. Our findings support current practice and further investigation of SBRT in patients with metastatic lung cancer.

This analysis also has several important limitations and challenges. In addition to the potential selection bias as discussed above, the study population is not a random selection of all cancer patients across the country; SEER data cover approximately 28% of all cancer patients, and some regions are not be represented in the sample. In addition, SEER-Medicare data only includes patients over the age of 65 and the results may not be applicable to younger lung cancer patients. While this could affect results, we feel the study is relevant for most cases of metastatic lung cancer given the prevalence of lung cancer among the elderly. In addition, SEER-Medicare does not contain data on patient performance status, which is a known independent prognostic factor for survival in lung cancer (38). That said, performance status is well approximated by disability status which we used in this study (31). Finally, given the time period available for study using this SEER-Medicare database (outcomes through 2014), we do not have any information regarding immunotherapy use, which has been shown in multiple randomized trials to improve overall survival in advanced-stage NSCLC, but whose practice-changing results were published after this study period (39-45). In addition, prospective data supporting the use of SBRT has accrued since this time (10-12). Nonetheless, there is growing evidence for clinical synergy between SBRT and immunotherapy, and thus it is plausible that a survival advantage with SBRT may improve with immunotherapy

(46-51). The combination of SBRT and immunotherapy in advanced stage NSCLC is currently being evaluated in prospective studies (52-57).

In conclusion, we observed increased use of SBRT from 2004 to 2013 and its use was associated with longer survival. Although fewer SBRT patients were hospitalized, there was an increased cost associated with hospitalizations that was primarily due to their longer survival. Our findings support the ongoing evaluations of SBRT in combination with systemic therapy in elderly patients with metastatic NSCLC.

Acknowledgments

Footnote

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Table S1 Diagnosis and procedure codes

Variables	Codes
Diagnosis (ICDO3)	
Adenocarcinoma	8140-7, 8255, 8260, 8310, 8480-1, 8490, 8560, 8570-1.
Bronchioalveolar carcinoma	8250-4
Squamous cell carcinoma	8070-8, 8050-2
Large cell	8012-3, 8022, 8033
Other/undifferentiated	All other codes associated with lung primary
SBRT codes	
ICD-9	92.3, 92.30-92.39
HCPCS	61793, 77371, 77373, 77435 G0173, G0251, G0338, G0339, G0340, 61793, 0082T
Systemic therapy codes	
ICD-9	V58.1, V58.11, V66.2, V67.2, 99.25
HCPCS	96400-96499, 96500-96599, 99555, J8510, J8520, J8521, J8530-J8999, J9000-J9999, C9415, G0355-G0363, S9329-S9331, S9379, Q0083-Q0085, C8953, C8954, C8955, J9390, J9305, J9170, J9035, J9265, J9060, J9062, C9418, J9045, J9201

ICDO3, International Classification of Diseases for Oncology, Third Edition Codes for Histologic Classification; SBRT, stereotactic body radiation therapy; ICD, International Classification of Diseases; HCPCS, Healthcare Common. Procedure Coding System.

Table S2 Admission diagnoses and frequencies for hospitalized SBRT and chemotherapy patients

Admission diagnosis code	SBRT		Chemo		Total	Diagnosis
	Count	%	Count	%		
78605	51	12	94	8	145	Shortness of breath
486	28	7	79	7	107	Pneumonia
78079	16	4	43	4	59	Other malaise and fatigue
78609	14	4	24	2	38	Other respiratory abnormalities
1629	12	3	73	6	85	–
49121	12	3	31	3	43	Obstructive chronic bronchitis with (acute) exacerbation
389	11	3	17	1	28	Unspecified septicemia
78650	<11	<3	19	2	29	Chest pain

SBRT, stereotactic body radiation therapy; Chemo, chemotherapy.